UCRL-AR-146022

Cancer Rates among LLNL Employees: 1974-1997 Final Report

Funded by DOE Office of Health Programs/ Epidemiology Surveillance Programs

Donald Whorton, M.D.
Dan Moore, Ph.D.
Jim Seward, M.D.
Kathleen Noonan, R.N.
Mortimer Mendelsohn, M.D.

November 6, 2001

U.S. Department of Energy

Lawrence
Livermore
National
Laboratory

DISCLAIMER

This work was performed under the auspices of the U. S. Department of Energy by the University of California, Lawrence Livermore National Laboratory under Contract No. W-7405-Eng-48.

Cancer Rates among LLNL Employees: 1974-1997

Table of Contents

Tables and Figures

Background

Lawrence Livermore National Laboratory (LLNL) is a research and development laboratory owned by the U.S. Department of Energy and operated by the University of California. The Laboratory, located approximately 45 miles east of San Francisco, employs about 7,500 individuals. Its primary mission is national security, including the development of nuclear weapons, and it has a wide range of energy, environmental and health-related scientific projects. Because this work uses radioactivity and other potentially hazardous processes and materials, there is a continuing interest in monitoring the health of this workforce. This paper is the result of a surveillance effort to update our understanding of the patterns of cancer incidence in this population.

In the mid-1970s, LLNL physicians, during routine periodic medical examinations, found an unusual number of cases of malignant melanoma of the skin (melanoma). At LLNL request, the State of California conducted a formal melanoma incidence study and showed a statistically significant increase in melanoma (Austin et al, 1981). Many studies ensued, as well as active programs to prevent and manage the disease at the Laboratory and among the families of employees. This report of cancer incidence is also an opportunity to review the status of melanoma among the LLNL employees.

Previous Studies

The 1981 Austin et al. study focused only on melanoma. Four years later, Reynolds and Austin (1985) published a cancer incidence survey of LLNL employees for time period 1969-1980. They reported on 49 invasive cancer sites and 11 *in situ* cancer sites. This study included all active employees between the ages of 20 and 69 who resided in the San Francisco-Oakland Standardized Metropolitan Statistical Area (SMSA) and who were covered by the Resource for Cancer Epidemiology (RCE).

The RCE was one of the original 10 Surveillance Epidemiology and End Results (SEER) cancer or tumor registries in the United States, funded by the National Cancer Institute (NCI). The RCE was established in 1969 and included the five counties that constituted the 1969 San Francisco-Oakland SMSA: Alameda, Contra Costa, Marin, San Mateo, and San Francisco.

For female employees, Reynolds and Austin expected 32.63 total cancer cases based on the 1973 to 1977 age- and gender-specific rates for the San Francisco-Oakland SMSA and the ages and gender of LLNL employees. They found 43 cancer cases with an observed/expected ratio of 1.32. There were three cancer sites with statistically significant excesses: melanoma (7 observed/1.35 expected), rectum and anus (4 observed/0.76 expected) and salivary gland (2 observed/0.19 expected).

For male employees, they expected 140.63 total cancer cases and found 134 for an observed/expected ratio of 0.95. There were two cancer sites with statistically significant excesses: melanoma (24 observed/6.46 expected) and other nervous system (3 observed/0.23 expected).

Further analysis by grouping various categories of radiosensitive cancers did not show any excesses. The highly radiosensitive group included cancers of the bone, thyroid and blood. The moderately radiosensitive group included cancers of lung and female breast.

While Reynolds and Austin confirmed the melanoma elevations in both females and males, overall cancer rates were essentially normal.

In 1984, Moore and Bennett reported on the mortality rates of LLNL employees for 1964-1979. They conducted a national search for death certificates, covering all active and former employees of both sexes. They used US national rates for comparison. Combining sexes and races, they expected 920 deaths for all causes and observed 543 deaths for a standardized mortality ratio (SMR) of 59. There were no statistically significant excesses, including melanoma with its SMR of 150. There were six (6) significant reductions, most notable of which included total cancer (SMR of 70), respiratory cancer (SMR of 62) and diseases of the circulatory system (SMR of 58). Similar results were obtained when the analysis was limited to white males or white females with an all cause SMR of 63 and 69 respectively.

Currently, Mendelsohn and Moore are completing a LLNL mortality study for the years 1984-1996. The methods are essentially the same except that the National Death Index was used to find and classify deaths. The results show similar reductions in all cancer SMRs for males and females, and even greater reduction in all cause SMR (46), and circulatory system SMR (40). A significant positive finding was two (2) deaths from testicular cancer with only 0.3 expected.

Thus, the mortality studies indicate that LLNL employees have lower than expected mortality, particularly from cancer and circulatory diseases. There is no increase in mortality from melanoma.

Melanoma Activities

LLNL established a melanoma task force that made an intensive effort to search the literature and to evaluate the Laboratory for possible occupational causes of melanoma. They searched for comparable occupational sites both within the Laboratory s geographic area and within the Department of Energy. The region of California is relatively high in melanoma, but they were unable to document institutional rates comparable to their own. The nearest counterpart to LLNL and almost its mirror image is the Los Alamos National Laboratory (LANL) in New Mexico. LANL reported low to normal melanoma rates, and in roughly the same time period, almost the same overall low mortality rates as LLNL. Extensive epidemiological data from other DOE sites have reported no unusual melanoma experience, with the possible exception of a very recent report by Schymura (2001) on employees of Brookhaven National Laboratory. The Brookhaven report shows a slightly elevated proportional incidence ratio for melanoma of less than 150 for males and less than 110 for females when compared to Nassau and Suffolk Counties.

.

Studies were also conducted assessing the pathologic aspects of the LLNL melanoma cases. A single, highly experienced melanoma pathologist reviewed all of the LLNL material using standardized diagnostic parameters. The LLNL melanoma lesions were found to be significantly thinner than the corresponding melanomas from the region. In addition data from the local health maintenance

organization found that presumptive lesions from LLNL employees and their family members were more frequently biopsied than corresponding lesions from other patients (Hiatt and Fireman, 1986).

A case-control study by Austin and Reynolds (1984) of 31 melanoma cases and 110 controls found the usual associations of melanoma with mole counts, body coloring and solar sensitivity, as well as several novel associations with nuclear-weapon activities at LLNL. Repeat analyses and follow-up studies consistently confirmed the association with personal characteristics but gave no consensus on the occupational correlates (Kupper et al, 1987; Austin and Reynolds, 1987; Schwartzbaum et al, 1990, 1994). Moore et al. (1997) expanded the study to 69 melanoma cases with 69 controls from LLNL using a detailed occupational interview and analysis. They too found the usual personal characteristics for melanoma susceptibility, but they found essentially no occupational correlates. Most importantly, they explained the disparity with the previous studies by showing that including the time-period of employment, particularly during the early history of the Laboratory, was crucial to the finding of no occupational differences between cases and controls.

In 1984, the LLNL Health Services Department established a clinic, staffed by a dermatologist, to provide periodic examinations for employees whose skin type is associated with elevated-risk. LLNL s Health Services Department tracks melanoma surveillance data. All invasive and *in situ* cases reported to the LLNL Health Services Department are collected. LLNL also initiated an institution-wide education campaign about melanoma, including informational mailings, a self-assessment procedure and medical screening by a dermatologist. There was also educational outreach to family members of employees.

The general understanding of malignant melanoma of the skin has also expanded over the 17 years since the implementation of melanoma screening program at LLNL. The incidence of malignant melanoma has been rising among the general population in the USA. In addition, the relationship between sunlight and the disease has now been clearly established.

California Cancer Registry

LLNL is located in Livermore in the eastern end of Alameda County. A sizable number of LLNL employees live east of the laboratory in San Joaquin and other counties. As the original study included residents of the five counties (Alameda, Contra Costa, Marin, San Mateo, and San Francisco), a surveillance project limited to residents of the five counties cited above would miss approximately 30 to 35 percent of current LLNL employees.

The State of California established the California Cancer Registry (CCR), effective 1988, as the statewide cancer incidence reporting system. The CCR collects data from all of the counties in which one would expect LLNL employees to reside. Using only the CCR data as a basis for a surveillance program, the program would be limited to a ten-year period (1988-1997), and all employees would be covered. The annual update of data from the CCR is released in August of each year, e.g., the 1997 data became available in August of 2000. At the time of our analysis, we used the most currently available data, i.e., the 1997 CCR data.

During the 1980s and 1990s the peak number of University of California LLNL employees was approximately 8,000. The current employee census is closer to 7,500. Since we were planning on

using data from both the SEER and CCR, we originally estimated the number of person-years to be 110,400 for males and 25,100 for females. Using these person-year estimates and the rates from the SEER and CCR, we projected a 4.3 fold increase in the number of person-years compared to the data reported by Reynolds and Austin. With an increase in person-years, we also expected to see a similar increase in the number of cancer incidence cases. Our study overlaps seven years (1974-1980) of the Reynolds and Austin 1985 study.

The CCR also collects cancer incidence data on selected *in situ* cancers. These include colon/rectum, melanoma and female breast cancers. The *in situ* cancer sites are included in the data analyses. The general definition of *in situ* cancers is those cancers, which are the earliest phase of cancer and have not extended beyond the surface tissues. Generally, *in situ* cancers can be completely treated by simple excision.

There were limitations associated with use of the CCR data due to confidentiality issues. The CCR did not permit us to release any specific cancer site data to LLNL in which the observed number of cases was less than six. During the course of this surveillance assessment, we abided by these data limitations: no data were discussed, presented, or released in which individual data cells had fewer than six cancer cases.

The proposal for this medical surveillance update was submitted to the LLNL Institutional Review Board (IRB) for its review. The IRB determined, based on criteria established in 10 CFR 745 Protection of Human Subjects, that this proposed medical surveillance assessment met the criteria as an exempt activity. This meant that the assessment was considered a part of the normal activities of the LLNL Health Services Department.

Methods for Cancer Surveillance Assessment

We conducted an update of cancer incidence experience of the LLNL employees, primarily in the years after the study done by Reynolds and Austin. We used the CCR to implement a comprehensive surveillance project for cancer incidence among LLNL employees. We used a 24-year period (1974 through 1997) for this surveillance assessment based on availability of personnel data from LLNL and availability of cancer incidence data from the CCR, including the previous SEER program data.

Based on availability of cancer incidence data, we used two sources for cancer incidence data: SEER between 1974-1987 and CCR between 1988-1997. The 14-year surveillance period from 1974-1987 included LLNL employees who were residents of the five counties comprising those in the SEER program (same data source as used by Reynolds and Austin). The 10-year surveillance period from 1988-1997 included all LLNL employees who were residents of California and thus covered by the CCR data.

For the analyses, we asked the personnel department of the laboratory to provide us a listing of all LLNL employees by year from 1/1/74 through 12/31/97. This listing included both those employees who resided in the five counties comprising the San Francisco-Oakland SMSA (Alameda, Contra Costa, Marin, San Francisco and San Mateo) as well as those who resided in

other counties. The five listed counties were included in the SEER program. The information we requested included: name, Social Security number, date of birth, date of initial employment and date of last employment.

LLNL's Health Services Department (HSD) obtained the data from the LLNL personnel department and submitted them to the CCR for matching with cancer incidence cases. An employee had to have six months of consecutive employment to be included. The CCR provided us with information on cancer cases without personal identifiers.

For the time period 1988-1997, we assessed the cancer incidence for all LLNL employees, including those residing in California both within and outside the five SEER counties. We requested the similar information cited above.

We submitted these data to the CCR and requested that they use data from 1974 through 1997 in its matching search. Since the cancer medical surveillance assessment was limited to individuals employed between 1974 and 1997 for six months or more and who resided within the State of California, we requested the CCR to limit matches to the period of time the individual was an active employee at LLNL. We elected not to attempt to assess cancer incidence occurring in former LLNL employees, as we had no effective methodology to assure comprehensive follow-up. We were limited to occurrence of cancer while the individuals were active employees.

We used the cancer incidence cases identified by SEER for the residents of the five counties comprising the SEER population for the analysis of the data from 1974 through 1987 and the cancer incidence cases identified by the CCR for the years 1988-1997. The CCR was able to combine the data from the SEER and CCR databases.

The data we received from the CCR contained no identifiers and were sent to one of us (DW). These data were not made available to LLNL personnel.

We analyzed the data for males and females separately. We did the following:

- Analyzed for total as well as individual cancer sites for each gender
- Conducted time-trend analyses for certain cancers
- Assessed radiosensitive cancers as defined in 1984 by Reynolds et al. (highly radiosensitive cancers of bone, thyroid and all leukemia except chronic lymphocytic leukemia (CLL) as well as moderately radiosensitive cancers of lung and female breast).
- Included *in situ* cancer sites in our analyses
- Combined analyses of invasive and *in situ* malignant melanoma by gender.

Results

A file containing 17,785 employees who had worked for six or more consecutive months at LLNL anytime during the time period 1/01/74 through 12/31/97 was submitted to the California Cancer Registry (CCR). The CCR, though its linkage techniques, identified 541 individuals with invasive cancer and 96 with *in situ* cancer. These employees provided 186,558 person-years of observation:

145,203 were from males and 41,355 were from females. Forty of the 17,785 employees had missing data and were excluded from the analyses.

In order for us to analyze the data, the CCR then submitted a file to us that did not contain identifiers, e.g., names or Social Security numbers. We calculated the expected number of cancer incidence cases by multiplying age and sex specific SEER rates by the LLNL person-years. We elected not to use the California cancer incidence rates since only between 20-30% of the employee population resided outside the SEER area during the assessment period, and individual employee residences were not known. Based on residence of the employees, the SEER rates were the more appropriate rates to use. Employees were considered at risk only while they were employed.

To obtain the population at-risk, we had to make several adjustments. We used the start year and termination year, along with the birth year, to estimate the population at risk in each five-year age and sex category for each calendar year. On average, an employee only works one-half of the start year and one-half of the termination-year. We adjusted the data by assuming that the start and termination years were a half-year each. This adjustment, a standard and accepted method, reduces the possibility for over-counting person-years of observation.

We made our second adjustment to account for county of residence. We used the San Francisco SEER registry for the years 1974-1987 and the statewide registry (CCR) for the years 1988-1997. Neither registry covered any employees living outside of the SEER registry area during the years 1974-1987. We used a report of employee residences for the years 1974-1987 to adjust for employees who lived outside the SEER registry area. This adjustment, also a standard method, assured us that we would not over count person-years. Over-counting person-years would inflate the expected number of cancers.

The number of LLNL employees increased annually from 1974 until 1989. With the exception of the year 1992, the number of employees has dropped each year since 1989. There has been an increase in the number of female employees as well as a change in the ratios of females to male employees over time. The percentage of females rose from 8% in 1974 to 28% in 1997. These annual data, expressed as person-years, are shown in Figure 1.

There were 637 individuals diagnosed with invasive and *in situ* cancers during the 24-year period 1974-1997: 437 males and 200 females. As shown in Table 1, there were 404 males found to have invasive cancer while another 33 were noted to have *in situ* cancer. For females, 137 were found to have invasive cancer while 63 were noted to have *in situ* cancer.

The age and gender distributions for individuals with cancer are shown in Table 2. The age group with the most cancers was the group 55-59 years of age. The age group with the least number of cancers was the group under age 30.

Table 3 shows the number of cancer cases, both invasive and *in situ*, diagnosed by calendar year. The numbers starting in 1988 reflect the results using the statewide registry. The previous years reflect data from the five-county SEER program.

We found a statistically significant deficit in the total number of invasive cancers for males (404) compared with the expected of 587.1. The standardized incidence ratio (SIR) was 69 (95% CI 62-76). There were only two invasive cancer sites with statistically significant excess: melanoma and cancer of the testes. For eight categories or cancer sites, we found a statistical deficit in cancer incidence. The most striking deficit occurred in cancer of the lungs and bronchus with a SIR of 36 (95% CI 26-50) with 38 observed compared with 104.7 expected. These data are shown in Table 4.

The results for *in situ* cancers for males are shown in Table 5. There was statistically significant excess for melanoma. There was a non-statistically significant deficit for all other *in situ* cancers combined.

For invasive cancer in females we found a statistically significant deficit in the total number of 137 compared with the expected of 171.0. The standardized incidence ratio (SIR) was 80 (95% CI 67-94). There was a statistically significant deficit for cancers of the female genital organs. There was a non-statistically significant excess for melanoma with a SIR of 165 (95% CI 88-281). These data are seen in Table 6.

The results for *in situ* cancers for females are shown in Table 7. Both breast and cervix cancers had elevated SIRs, but neither of these elevations was statistically significant. There were statistically significant excesses for all other *in situ* cancers.

In our assessment of cancer incidence among LLNL employees, we found statistically significant deficits for total invasive cancers in both males (SIR 69) and females (SIR 80). On the other hand, we found statistically significant elevations for *in situ* cancers for both males (SIR 196) and females (SIR 152). Since *in situ* cancers are considered to be cancers in their earliest phase, one would expect most *in situ* cancers to become invasive cancers if not recognized and treated. As such, to assess the total cancer incidence among LLNL employees, we combined the *in situ* with the invasive cancers. As shown in Table 8, the combined SIR of 72 for males is still significantly lower than expected (95% CI 66-79, $p<0.0001$). The combined SIR of 94 for females still is a deficit but is no longer is statistically significant (95% CI 81-107, $p=0.40$).

Individual Cancer Site Analyses

Because of the limitations due to the confidentiality considerations of the CCR, some of the results on specific cancers are limited to general statements without specific data. The data are available, but we cannot show all of them per our agreement with the CCR. For some cancer sites, we have combined the male and female cancer results to overcome this limitation and to provide more robust data.

Melanoma

There were 84 cases of invasive and *in situ* melanoma in both genders. The SIRs for both invasive and *in situ* melanoma were statistically elevated in males and non-statistically elevated in females. We conducted additional analyses in order to assess further the melanoma data.

We examined time-trends for melanoma by dividing the 24-year observation period into eight (8) three-year groupings. We calculated the combined invasive and *in situ* SIRs and 95% confidence intervals for each of these grouping.

We found that each of the combined SIRs showed a statistically significant increase during the first four time-periods: 1974-76, 1977-79, 1980-82 and 1983-85. The SIRs for the time-periods 1986-88 and 1989-91 were both above 100, but neither one was statistically significant. The SIRs for the last two time-periods (1992-94 and 1995-97) were both less than expected although neither deficit was statistically significant. These data are shown in Table 9 and Figure 2. When we tested a time-trend analysis for the years 1974-97, we found a statistically significant decrease ($p<0.001$).

As described previously, LLNL maintains surveillance data of invasive and *in situ* melanoma cases. We compared the surveillance data to the data we received from the CCR.

For invasive melanoma, the comparison between the LLNL surveillance data and the CCR data are shown in Table 10. The LLNL surveillance data contains two cases in addition to those in the CCR data set, but two of those cases were diagnosed at a time when each of the individuals was living outside of California. As such, neither of these cases would have been reported to the CCR. The other difference in the table most likely represents a discrepancy in reporting year.

For *in situ* melanoma, a much larger discrepancy was found as there were 34 cases in the LLNL surveillance data compared to 24 for the CCR. There were five additional cases in the LLNL surveillance data compared to the CCR for each of the two-twelve-year time-periods: 1974-85 and 1986-97. This difference between the LLNL surveillance data and the CCR data has been consistent over time of this assessment. The LLNL surveillance data appears to be the more sensitive method for case ascertainment.

We examined the differences between the LLNL surveillance data and the CCR reported data using the calculated annual SIRs for each data set for invasive and *in situ* melanoma separately. Figure 3A shows the graphic representation of the melanoma invasive and *in situ* data for the LLNL surveillance data, while Figure 3B shows the data for the CCR data.

For the LLNL surveillance data, the SIRs for invasive melanoma have been less than expected since 1988. The *in situ* SIRs have dropped markedly since the peak in 1984 and now approach the expected SIR of 100. For the CCR data, we see a similar pattern except that the SIR for *in situ* melanoma has also dropped below the expected SIR of 100.

In summary, the excess in melanoma found in the 1970s among LLNL employees no longer exits. LLNL employees now have fewer melanoma cases (combined invasive and *in situ*) than the expected based on the SEER rates. This is true for both the LLNL surveillance data and the CCR data.

Testicular Cancer

We found 21 individuals with testicular cancer compared to the 10.1 expected. The elevated SIR of 207 (95% CI 129-317) was statistically significant. We looked at various parameters to evaluate this excess further.

We first looked at age of diagnosis. There were 14 cases among men under age 40 and seven cases in men 40 and older. Based on the SEER rates for the 21 observed cases, we would have expected 12.9 to be under age forty and 8.1 to be over age forty. The age distribution of the observed testicular cancer cases is not different from expected.

We examined the cell type (histology) of the testicular cancers. Thirteen (13) or 62% were seminomas, while the remaining 8 (38%) had other cell types. Using the SEER data, we would have expected 57% to be seminomas and 43% to have other cell types. There were essentially no differences in cell type or histology from the expected.

We examined the calendar year of diagnosis to assess the time-trend for testicular cancer by using annual SIR results. As shown in Figure 4, we found an increase in testicular cancer among LLNL employees. We also tested whether time affected the histology (cell type) or age distribution of cases. We found no statistical correlation for either.

Bladder Cancer

There were 32 combined invasive and *in situ* bladder cancers among male LLNL employees compared to 29 expected. The slightly elevated SIR of 110 (95% CI 76-156) was not statistically significant. There was slight excess among men less than 50 years of age (7 observed compared to 4.9 expected). The results for individuals aged 50 years and older showed 25 observed compared to 24.1 expected. The differences in the age distribution were not statistically significant ($p = 0.32$).

We combined results from both males and females for both invasive and *in situ* bladder cancer and calculated annual SIRs. As shown in Figure 5, time-trend analysis for combined invasive and *in situ* showed considerable variations over time.

Prostate Cancer

There were 87 observed prostate cancers compared to 82.6 expected for a SIR of 105 (95% CI 83-127). The average age for LLNL cases is 57 with the SEER being 59. This difference is not statistically significant. The time-trend analysis in Figure 6 of annual SIRs shows variation over time.

Colon/Rectal Cancer

There were 51 colon/rectal cancers among male LLNL employees compared to the 66.6 expected for a SIR of 77 (95% CI 57-101). There were 32 colon cancers compared to 42.5 expected for a SIR of 75 (95% CI 52-106). For rectal/anal cancers, there were 19 observed compared to 24.1 expected for a SIR of 79 (95% CI 47-123).

There were 10 invasive and *in situ* cancers for female employees compared to the 6.4 expected for a SIR of 156 (95% CI 75-287). For rectal and anal invasive and *in situ* cancers for female employees, there were six observed compared to 3.63 expected for a SIR of 165 (95% CI of 61-359).

There was an overall deficit in the number of cases compared to the expected. The annual SIR time-trend analysis, as seen in Figure 7, shows a slight increase in the SIRs for the late 1980s and early 1990s followed by a consistent decline.

Breast Cancer

There were 54 invasive and 12 *in situ* breast cancers among female employees compared to 58.5 and 7.9 expected. The SIR for invasive breast cancer was 92 (95% CI 69-120) and for *in situ* breast cancer was 120 (95% CI 62-209).

Histological analysis for invasive cancers showed that both the observed and expected were the same with 70% due to ductal cancer. For the *in situ* cases, 50% of the observed were due to comedocarcinoma whereas only 26% of the expected from the SEER data were expected to be this cell type (p=0.075).

Among the LLNL employees, 75% of the *in situ* cases occurred in women younger than 50 years of age compared to a 50% expected SEER rate (p=0.13). For invasive breast cancer the percentages for women younger than age 50 was 46% for LLNL employees and 55% for the SEER expected (p=0.12). The laboratory employees with *in situ* cancer tended to be younger than the expected, whereas for invasive cancer, the opposite was the trend.

The annual SIR time-trend analysis for the combined invasive and *in situ* breast cancer shown in Figure 8 depicts an almost consistent deficit of breast cancer among LLNL female employees.

Cervical Cancer

There were 38 *in situ* cervical cancers compared to 28.2 expected. There were fewer than six invasive cervical cancers during the observation period. In fact, there have been no invasive cervical cancer cases among LLNL employees since 1984. The combination of *in situ* and invasive cervical cancer showed a statistically significant deficit with a SIR of 67 (95% CI 48-91).

The age distribution for *in situ* and invasive cancer showed that 37% of the LLNL women were under age 30 compared to 23% of the SEER reference data. This difference is statistically significant (p=0.035). The *in situ* SIR for LLNL women under age 30 was statistically significant with a SIR of 218 (95% CI 120-364). For women 30 years and older, the SIR of 110 (95% CI 71-163) was elevated but not statistically significant.

The CCR stopped collecting *in situ* cervical cancer in 1995. There had been a fourfold increase in the SEER rates for *in situ* cancer during the time period 1975-1994. The LLNL rates for *in situ* cervical cancer were consistently 20-40% higher than the SEER rates prior to 1990, but since 1990

these rates have been lower than the SEER rates. The reasons for these trends in the *in situ* cancer over time are unclear.

Cervical cancer can be detected in its early phases by use of periodic cervical Pap testing. Ideally, positive Pap test results should allow for treatment in the early phases of cervical cancer thus preventing continuation of the process to become invasive cancer.

Most striking is the extremely low rate for invasive cervical cancer rates among LLNL employees. The SIR time-trend analysis for invasive cervical cancer is shown in Figure 9. These data would appear to reflect success of cervical cancer screening.

Lung Cancer

Cancer of the lungs and bronchus were strikingly low in males with an SIR of 38. The SIR of 79 in females was also lower than expected but was still more than double that of males. The low lung cancer results may be due to the lowered smoking rates among LLNL employees. In a sample of 735 employees who self-reported for a preventive health check-up, only 6.3% were smokers. Differential smoking rates between male and female employees would be one possible explanation for the different ratios for lung cancer between the two genders. Currently, however, there are insufficient data to assess this possibility.

Brain Cancer

There were 12 brain cancers compared to 12.1 expected. The histological diagnosis of eight (8) of the brain cancer cases was glioblastoma multiforme. This compared to six expected glioblastoma multiforme based on the SEER rates.

Cancer of the Eye

There were fewer than 6 cancers of the eye among the LLNL employees. The SIR for both invasive and *in situ* combined of 230 (95% CI 63-589) was not statistically elevated.

Radiosensitive Cancers

We analyzed the data using the same radiosensitive cancer categories described by Reynolds and Austin. The highly radiosensitive cancers consisted of bone cancer, thyroid cancer and all types of leukemia except for chronic lymphocytic leukemia (CLL). The moderately radiosensitive cancers consisted of female breast and lung cancer. The low or non-radiosensitive cancers were the remaining ones. We had to combine males and females for the highly sensitive cancers but were able to analyze the other two categories separately by gender. Table 11 shows that there were no increases in any of these groupings.

In our assessment of cancer incidence among LLNL employees, we found statistically significant deficits for total invasive cancers in both males and females, but statistically significant elevations for *in situ* cancers for both males and females. The increase in overall *in situ* cancer rates was primarily due to the elevated *in situ* melanoma results. The combined SIR for invasive and *in situ* cancers cancer still show a statistically significant deficit for males and a non-statistically significant deficit for females. We showed a larger deficit in cancer incidence cases for males than did Reynolds and Austin. Where Reynolds and Austin reported an excess of cancer for females, we show a cancer deficit.

Very low rates for lung cancer, especially among men, were found. The lung cancer deficit is insufficient to explain the overall low cancer rates. For males, there were 183.1 fewer total cancers found than expected, whereas there were 62.7 fewer lung cancers than expected. After removing lung cancers, there were 120.4 fewer cancers than expected. The SIR without lung cancer is 75.9.

The lung cancer rate in females was not an important factor in the lower observed cancer results. There were 34 fewer total cancers than expected, but there were only 2.5 fewer lung cancers than expected. After removing the lung cancers, there were 31.5 fewer cancers than expected. The resulting SIR is 80.2.

We found that melanoma was still elevated but that the elevations were due to cancers that occurred prior to 1992. Since 1992, the combined invasive and *in situ* LLNL rates for melanoma are lower than the SEER comparison rates. The trend as shown in Table 9 and Figure 2 shows a continuing decrease in melanoma cases among LLNL employees since 1986.

The surveillance data collected by the LLNL Medical Department shows almost identical data to the CCR data for invasive melanoma. The LLNL surveillance data have 40% more cases for *in situ* cancer compared to the CCR data. The increase *in situ* melanomas may be a result of the melanoma clinic and data collection. It also may be due to differences in reporting criteria for the LLNL surveillance data compared to the CCR. For whatever the reason, the LLNL surveillance data have consistently had more *in situ* cases than the CCR.

We conducted analysis of melanoma using first the CCR data and then the LLNL Surveillance data. We found higher SIR using the LLNL surveillance data compared to the CCR data. The CCR expected rates are based on its criteria for reporting melanoma. If one uses the different and apparently more sensitive criteria, the results must be higher than the conventional method. If we assume that the CCR had the same criteria as the LLNL s surveillance data, then the CCR expected rates would be correspondingly higher. With higher expected rates (denominator) and correspondingly higher observed rates (numerator), the SIR should be similar to using conventional rates.

We found that using the conventional CCR methodology, the combination of invasive and *in situ* melanoma have been less than the expected since 1992. When we then used the data from the LLNL surveillance information, we found that, since 1994, the observed cases of melanoma were less than the expected.

These data indicate that the increased number of melanoma cases among LLNL employees has disappeared and the rates are now actually lower than the expected. This decrease may be due to the increase protection against sunlight as a result of the melanoma educational information and screening programs.

We found a statistically significant increase in testicular cancer. The increase in testicular cancer is similar in magnitude as to that reported by Reynolds and Austin. We observed 21 cases for an SIR of 207, whereas Reynolds and Austin reported observing seven (7) cases for an SIR of 224.

There are some recognized risk factors for testicular cancer. Most importantly, there is an observed relationship between the relative risk for testicular cancer for men in white collar and professional occupations. This relative risk ranges from 1.5 to 2.5 times greater than men in other occupational groups (Schottenfeld 1996). While the underlying cause for the elevated risk is unknown, this association with white collar and professional groups is one possible explanation for the LLNL increase.

Other recognized risk factors for testicular cancer include cryptorchidism (undescended testicle), prenatal exposure to exogenous estrogens, and familial and hereditary factors, e.g., chromosomal disorders. In the USA, there is a peak in testicular cancer incidence between ages 25 to 34 among white males of higher economic status. (Schottenfeld and Fraumeni, 1996). In a report on cancer among current and former Brookhaven National Laboratory Workers, Schymura reported an excess proportional incidence rates for combined cancers of the testis and other male genital organs. Schymura reported that the rates for combined male genital organs are lower than the rates among LLNL employees; however, Schymura does not specifically report on testicular cancer.

When we looked at age at diagnosis, time-trend, and histology, we only noted that there is a slight increase in rates compared to the SEER rates since 1984. Apart from the association with socio-economic status, we found no ready explanations for the increase in testicular cancer. Any additional investigations of testicular cancer among LLNL employees will require different methodologies than used in this assessment. The LLNL Health Services Department will need to develop an educational and screening program for testicular cancer.

Similar to the findings by Reynolds and Austin, we found no increase in any of the radiosensitive cancers. One of our most striking observations is the low lung cancer rate among male employees. While Reynolds and Austin found similar lung cancer results, they reported a SIR of 54, which is considerably greater than is our SIR of 36. Low cigarette smoking patterns, especially among the male employees, is the most obvious reason for the low lung cancer rates

Invasive cervical cancer has essentially disappeared among LLNL employees. The best explanation for this observation is the effectiveness of cervical cancer screening.

In summary, we found the following among the LLNL active employee group.

- There is considerably less cancer than expected
- Males have relatively fewer cancers than do females

- Lung cancer rates in males is remarkably low
- The rates for melanoma have dropped to lower than the expected rates over the past six years
- Testicular cancer rates are modestly elevated and appear to have been so for the past 20 years
- Lifestyle patterns, including smoking, and cancer screening activities are probably important contributors to the observed low cancer rates.

We are indebted to Mark Costella, Ed Cunniffe, Marleen Emig, John Futterman, Don Graves, Barbara Kornblum, and Lynda Seaver who participated in the LLNL Employee Advisory Group, for their advice and insight; Cliff Strader, Bonnie Richter, Heather Stockwell of the DOE Office of Health Programs for their funding and support; Bob Schlag, Sandy Liu, and Bill Wright of the California Cancer Registry; and Joe Bartelt, LLNL Administrative Information Systems.

Glossary

Cancer Incidence Rate

The number of newly diagnosed cases of cancer divided by the population during a one-year period

Cancer Mortality Rate

The number of cancer deaths divided by the population during a one-year period

California Cancer Registry (CCR)

The name of the cancer registry for the State of California in the Department of Health Service with headquarters in Sacramento

Case-Control Study

This is a study in which individuals with a condition or disease (cases) are compared to a similar group without the condition or disease (controls). The investigator assesses various attributes in the two populations.

Cohort Study

A defined population is followed over time to assess the outcomes of interest. The outcomes are compared to another population, often a national or state database.

Confidence Interval (CI)

The comparison between the observed divided by the expected value provides a point estimate of the incidence ratio. The confidence limits describe the range of values that are consistent with the observed ratio.

For example, in human studies, the results those are considered to be statistically significant if the observed relationship would occur by chance less than five percent (5%) of the time. If the specific level for confidence is defined as occurring less than five percent of the time by chance, then the confidence limits includes the point estimate and all values that would not occur by chance 95% of the time. This would be considered the 95% confidence interval (95% CI).

***In Situ* Cancer**

These are the earliest phases of cancers in which the specific cancer has not extended beyond the surface tissues. Generally *in situ* cancers can be completely treated by simple excision.

Invasive Cancer

These are cancers that have extended past the surface tissue to deeper aspects of the tissue. The cancer can invade deeper into its location of origin and may also invade other tissues or parts of the body.

Institutional Review Board (IRB)

A mandated committee within the organization established to review all proposed studies on human to assure safety of the participants. This is mandated per 10 CFR 745 Protection of Human Subjects.

Melanoma

A cancer of the skin characterized by dark pigmentation. These frequently will start with moles. Melanoma can spread from the skin to other parts of the body.

National Death Index (NDI)

The National Center for Health Statistics collects death certificates from all states and other jurisdictions. Since its establishment in 1979, it can search lists of names to determine who have died. Causes of death can be then obtained from the death certificates. Researchers involved in mortality studies frequently use it.

Person-Year

A unit of measurement that combines persons and time. A person-year is the observation of one person for one year. In the assessment, each person contributes only as many years of observation to the LLNL population at risk as he/she is actually observed (time as an active employee).

Proportionate Incidence Ratio

The number of different types of cancer cases in the total number of cancer cases observed. In these types of analyses, the denominator that is required in standardized cancer incidence studies is not used. This can lead to misleading conclusions if used to compare cancer incidence experience of populations with different distribution of cancer.

p Value

The letter p is used to show the probability that the results of the comparison could have occurred by chance if the groups are really alike.

Resource for Cancer Epidemiology (RCE)

The name of the five county cancer registry started in 1969 that was originally funded by the National Cancer Institute. The registry is operated by the California Department of Health Services and includes these five counties: Alameda, Contra Costa, Marin, San Francisco and San Mateo.

SEER

The name of the initial cancer registries funded by the National Cancer Institute in 1969. The name is Surveillance Epidemiology and End Results

Standard Incidence Ratio (SIR)

The ratio of the number of cancer cases observed in the study population to the number of cancers expected from the comparison population. This is also called an incidence ratio or point estimate. In order to eliminate decimal points, the SIR in the report has been multiplied by 100 or is expressed as a percent.

Standard Mortality Ratio

The ratio of the number of deaths observed in the study population to the number of deaths expected from the comparison population. This is also called a risk ratio or point estimate.

Statistical Significance

For most biomedical and epidemiology studies, a study result whose probability value (p-value) is less than five percent (<5%) is considered sufficiently unlikely to have occurred by chance and justifies the designation " statistically significant.

Cancer Rates among LLNL Employees: 1974-1997

References

Austin D, Reynolds P, Synder M, Biggs M and Stubbs HA (1981). Malignant melanoma among employees of the Lawrence Livermore National Laboratory. *Lancet* (October 3, 1981), 712-716

Austin D and Reynolds P (1984). A case-control study of malignant melanoma among Lawrence Livermore National Laboratory employees. Malignant melanoma, Report #3, UCRL-15629.

Austin DF and Reynolds P (1987). Investigation of an excess of melanoma among employees of Lawrence Livermore National Laboratory. *Am J Epidemiology* 145:524-534

Hiatt R and Fireman B (1986). The possible effects of increased surveillance on the incidence of malignant melanoma. *Prev Med* 15:652-660

Kupper L, Setzer RW, Schwartzbaum J and Janis J (1987). A case-control study of malignant melanoma among LLNL employees: a critical evaluation. UCRL-15928

Mendelsohn M (personal communication).

Moore DN and Bennett D (1984) Mortality among employees of the Lawrence Livermore National Laboratory. *Energy and Technology Review* (Dec) 9-19

Moore DN, Patterson HW, Hatch F, Discher D, Schneider JS, Bennett D and Mendelsohn ML. (1997). A case-control study of malignant melanoma among Employees of the Lawrence Livermore National Laboratory. *Am J Industrial Med* 32:377-391

Reynolds P and Austin D (1985). Cancer incidence among employees of the Lawrence Livermore National Laboratory, 1969-80. *West J Med* 142:214-218

Schottenfeld D and Fraumeni, Eds. (1996) *Cancer Epidemiology and Prevention*. Chapter on Testicular Cancer, Second Edition 1207-1219

Schwartzbaum J, Setzer R and Kupper I (1990). An exploratory analysis of the occupational correlates of large pigmented nevi at Lawrence Livermore National Laboratory. *J Occup Med* 32:6054-611

Schwartzbaum J, Setzer R and Kupper I (1994). Exposure to ionizing radiation and risk of cutaneous malignant melanoma. *Annals of Epidemiology* 4:487-496

Schymura MJ. (2001) Distribution of cancer among former and current Brookhaven National Laboratory Workers. New York State Department of Health. *http://tis.ch.doe.gov/epi/*

Table 1

Number of Invasive and *In Situ* Cancers by Gender
LLNL Medical Surveillance Program
1974-1997

Gender	Number of Invasive	Number of In Situ	Total
Males	404	33	437
Females	137	63	200
Total	541	96	637

Table 2

Number of Invasive and *In Situ* Cancers by Age and Gender
LLNL Medical Surveillance Program
1974-1997

Age Groups	Males	Females	Total	%
<30	10	20	30	4.7
30-34	21	13	34	5.3
35-39	15	17	32	5.0
40-44	37	34	71	11.1
45-49	47	28	75	11.8
50-54	78	39	117	18.4
55-59	104	29	133	20.9
60-64	75	11	86	13.5
65+	50	9	59	9.3
Total	437	200	637	

Table 3

Year of Diagnosis for Invasive and *In Situ* Cancers
LLNL Medical Surveillance Program
1974-1997

Year	Number	Cumulative
1974	10	10
1975	9	19
1976	13	32
1977	25	57
1978	12	69
1979	24	93
1980	24	117
1981	26	143
1982	13	156
1983	24	180
1984	24	204
1985	35	239
1986	22	261
1987	35	296
1988	34	330
1989	32	362
1990	45	407
1991	34	441
1992	45	486
1993	32	518
1994	33	551
1995	29	580
1996	30	610
1997	27	637

Note: Beginning in 1988, the data source is the California Cancer Registry

Table 4

Invasive Cancers for Male Employees
LLNL Medical Surveillance Program
1974-1997

No.	Cancer Group	Observed	Expected	SIR	95%CI	P value
1	Oral Cavity & Pharynx	14	35.0	40	22 - 67	<0.01
12	Digestive System	81	122.4	66	52 - 81	<0.01
14	Stomach	12	15.6	77	40 - 134	0.44
16	Colon & Rectum	51	66.6	77	57 - 101	0.06
36	Pancreas	14	13.4	104	57 - 175	0.94
40	Respiratory System	49	121.8	40	30 - 53	<0.01
42	Larynx	7	13.2	53	21 - 109	0.10
43	Lungs & Bronchus	38	104.7	36	26 - 50	<0.01
48	Skin excluding Basal & Squamous cell	51	71.9	71	53 - 93	0.01
49	Melanomas of Skin	47	34	138*	102 - 184	0.04
61	Male Genital System	109	89.9	121	98 -144	0.06
62	Prostate	87	82.6	105	83 - 127	0.66
63	Testes	21	10.1	207*	129 - 317	<0.01
66	Urinary System	34	45.6	75	52 - 104	0.09
67	Urinary Bladder	32	29.0	110	76 - 156	0.63
68	Kidney & Renal Pelvis	10	15.4	65	31 - 119	0.20
72	Brain & Other Nervous	12	12.2	98	51 - 171	0.54
75	Endocrine System	7	7.3	96	39 - 197	0.55
78	Lymphomas	24	41.9	57	37 - 85	<0.01
82	NHL	21	36.0	58	36 - 89	<0.01
86	Leukemias	9	14.3	63	29 - 119	0.19
	All Other Cancers	14	24.8	56	31-94	0.03
	Totals	404	587.1	69	62 - 76	<0.01

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 5

In Situ Cancers for Male Employees
LLNL Medical Surveillance Program
1974-1997

No.	Cancer Group	Observed	Expected	SIR	95% CI	P value
49	Melanoma of Skin	20	7.5	266*	163 — 411	<0.01
	All Others	13	9.3	140	75 — 239	0.29
	Total	33	16.8	196*	135 - 276	<0.01

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 6

Invasive Cancers for Female Employees
LLNL Medical Surveillance Program
1974-1997

No.	Cancer Group	Observed	Expected	SIR	95% CI	P value
12	Digestive System	16	14.7	108	62 — 177	0.80
16	Colon & Rectum	12	9.1	132	68 — 229	0.41
40	Respiratory System	11	12.3	89	45 — 160	0.86
43	Lungs & Bronchus	9	11.5	79	36 — 149	0.58
48	Skin excluding Basal & Squamous cell	13	8.3	157	84 — 268	0.16
49	Melanomas of the Skin	13	7.9	165	88 — 281	0.12
51	Breast	54	58.5	92	69 — 120	0.61
52	Female Genital Organs	24	53.9	45	29 — 66	<0.01
54	Corpus & Uterus, NOS	9	9.9	91	42 — 173	0.94
57	Ovary	7	6	110	47 — 240	0.79
78	Lymphomas	6	4.5	133	49 — 290	0.59
	All Others	13	18.8	69	37 — 118	0.21
	Totals	137	171	80	67 — 94	<0.01

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 7

In Situ Cancers for Female Employees
LLNL Medical Surveillance Program
1974-1997

No.	Cancer Group	Observed	Expected	SIR	95% CI	P value
51	Breast	12	7.9	152	79 — 264	0.21
53	Cervix	38	28.2	135	95 — 185	0.09
	All others	13	5.2	248*	134 — 427	<0.01
	Total	63	41.3	152*	115 - 190	<0.01

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 8
Combined SIR for Invasive and In Situ Cancers for Both Males and Females
LLNL Medical Surveillance Program
1974-1997

Category	Males			Females		
	O/E	SIR	95% CI	O/E	SIR	95% CI
Invasive	404/587.1	69	62 — 76	137/171	80	67 — 94
In Situ	33/16.8	196*	135 - 276	63/41.3	152	115 — 190
Total	437/603.9	72	66 - 79	200/212.3	94	81 - 107

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 9

Comparison of Annual SIRs for Invasive and *In Situ* Melanoma for Males and Females
LLNL Medical Surveillance Program
1974-1997

Year Grouping	Observed	Expected	SIR	95% CI	P value
1974-76	9	2.2	409*	188 — 777	<0.01
1977-79	9	3.5	257*	118 - 488	0.02
1980-82	10	4.3	230*	111 — 423	0.03
1983-85	19	5.8	326*	195 — 507	<0.01
1986-88	9	8.2	109	50 — 207	0.87
1989-91	14	9.4	149	82 — 249	0.19
1992-94	6	9.8	62	23 — 134	0.29
1995-97	8	10.9	73	32 — 145	0.48

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Table 10

Comparison of LLNL Medical Department s Surveillance Roster to CCR Data for Invasive Malignant Melanoma
LLNL Medical Surveillance Data
1974-1997

Years	LLNL Data	CCR Data
1974-78	16	14
1979-83	17	18
1984-88	12	12
1989-93	11	10
1994-97	6	6
Total	62	60

Table 11

Radiosensitive Cancers by Gender
LLNL Medical Surveillance Program
1974-1997

Category	Gender	Observed	Expected	SIR	95% CI	P value
High	Both	15	23.9	63	35 - 104	0.07
Moderate	Males	40	121.4	33	24 - 45	<0.01
	Females	63	70.8	89	65 - 109	0.39
All Others	Males	352	448.2	79	70 - 87	<0.01
	Females	71	93.9	76	49 - 82	0.02

*** Statistically significantly elevated SIR at p<0.05**
Statistically significantly lowered SIR at p<0.05

Figure 1

Person-Years by Gender
1974-1997

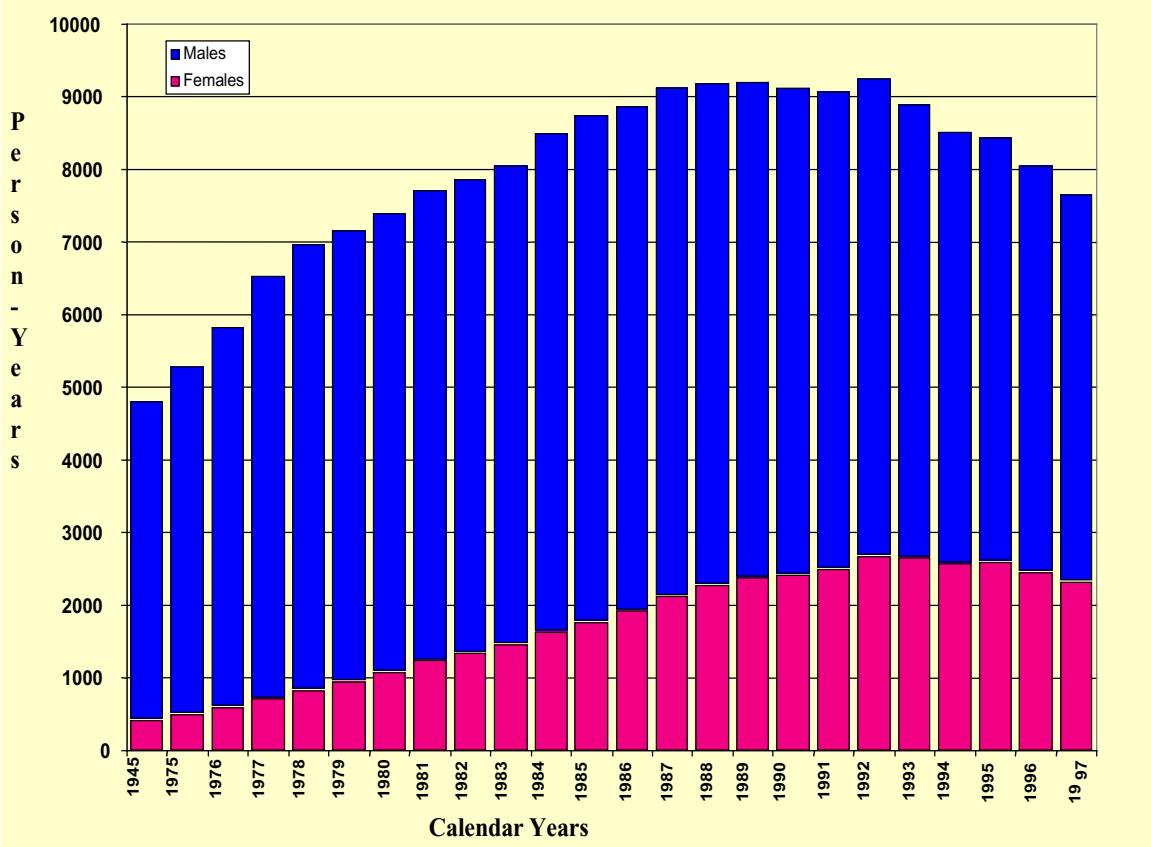
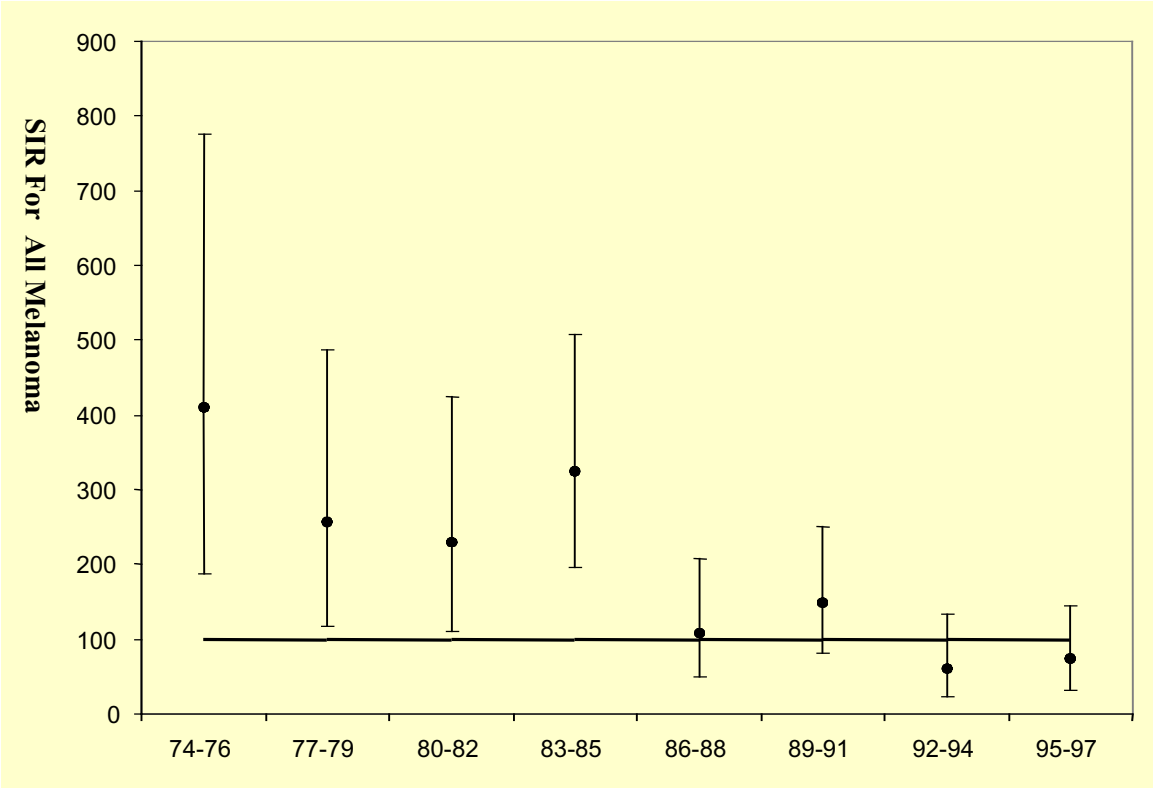


Figure 2

Invasive and *In Situ* Melanoma Combined Standard Incidence Ratios (SIRs) by Eight Three-year Time-Periods 1974-1997



Bars are 95% confidence intervals for the SIR.

Figure 3A

Standard Incidence Ratios (SIRs) for Invasive, *in situ* and Total Melanoma Cases Reported to CCR 1974-1997

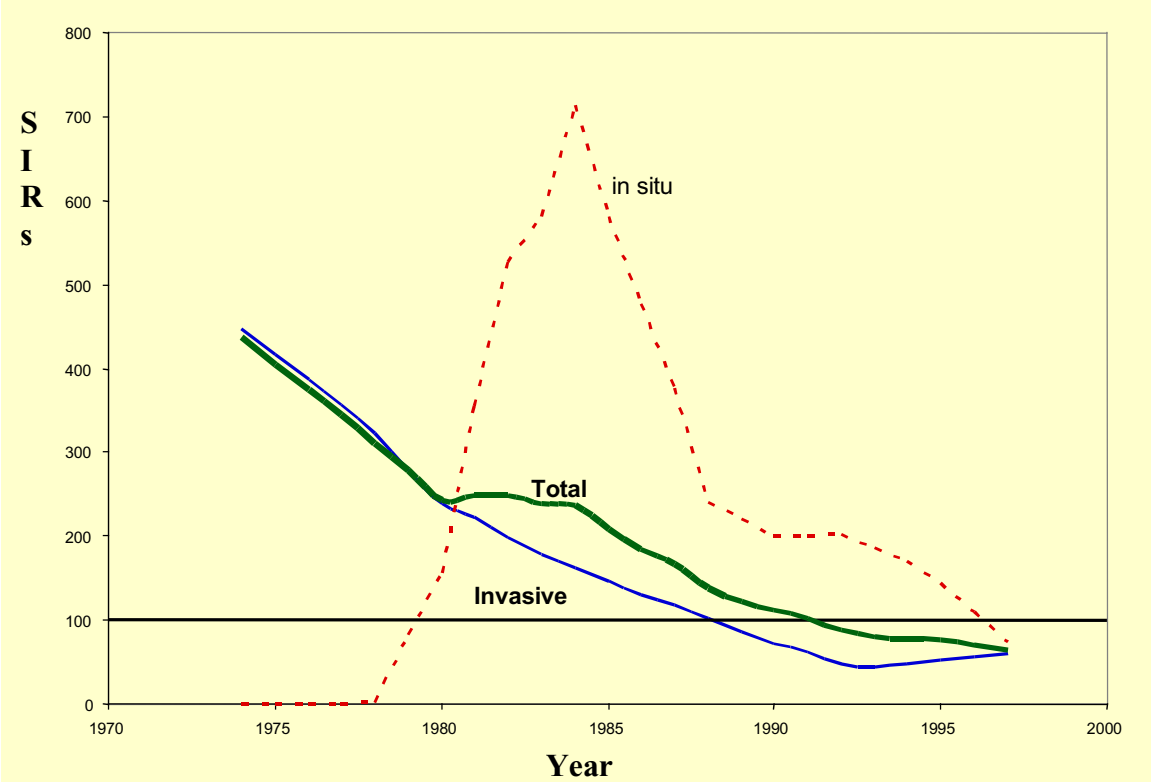


Figure 3B

Standard Incidence Ratios (SIR) for Invasive, *in situ* and Combined Melanoma Cases from LLNL Surveillance Data

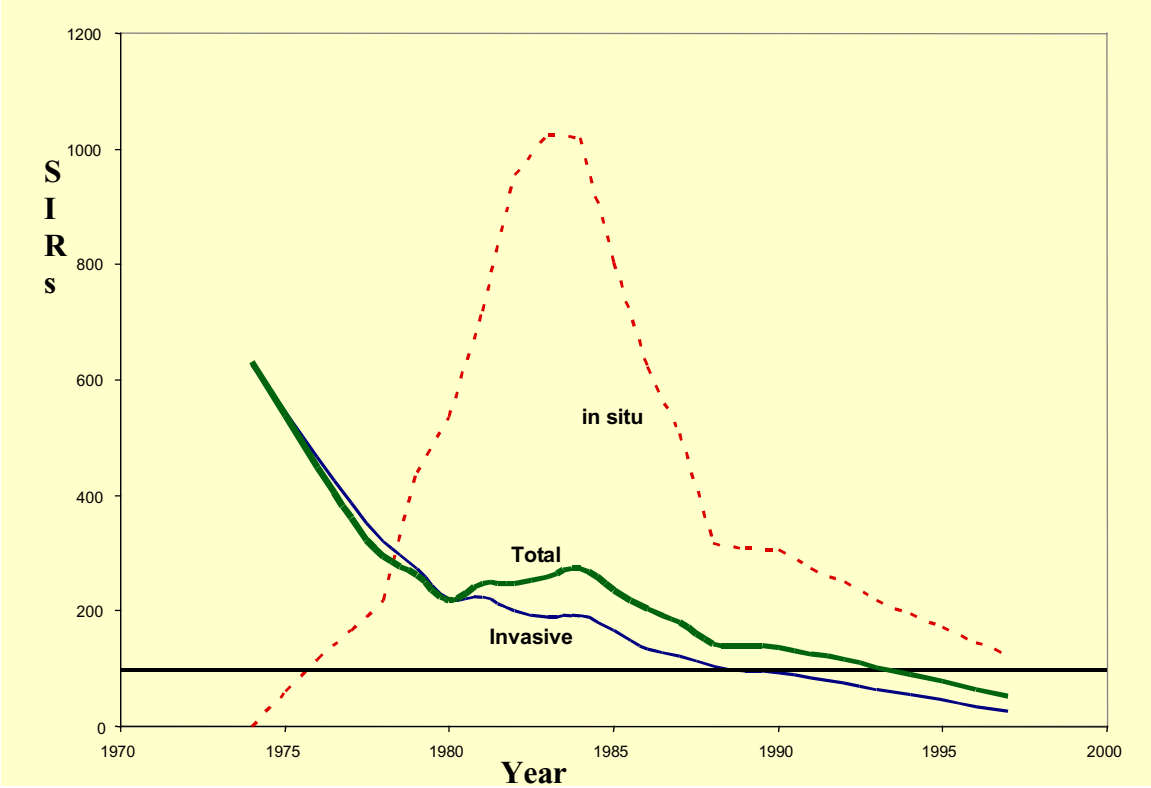


Figure 4

Standard Incidence Ratios (SIRs) for Testicular Cancer 1974-1997

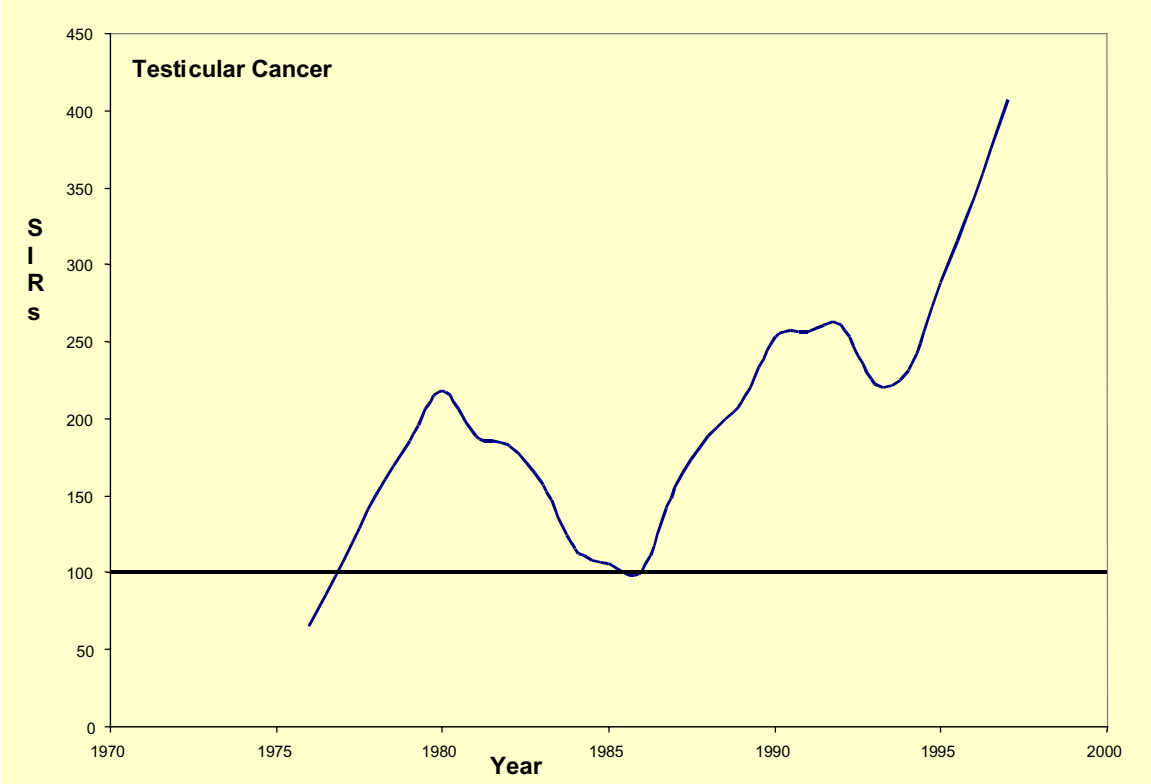


Figure 5

Standard Incidence Ratios (SIRs) for All Bladder Cancer
Males and Females Combined
1974-1997

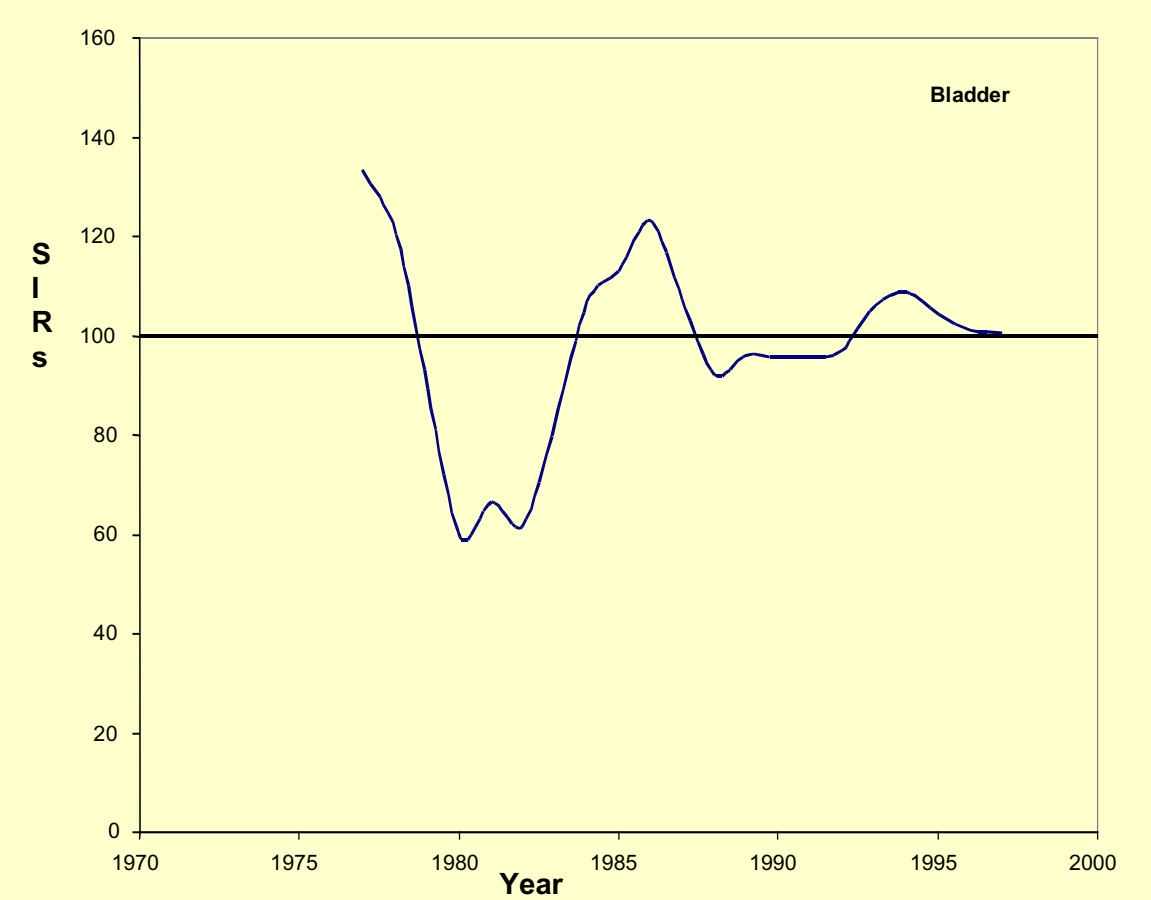


Figure 6

Standard Incidence Ratios (SIRs) for Prostate Cancer 1974-1997

Figure 7

Standard Incidence Ratios (SIRs) for All Combined Colon and Rectal and Anal Cancers
Males and Females Combined
1974-1997

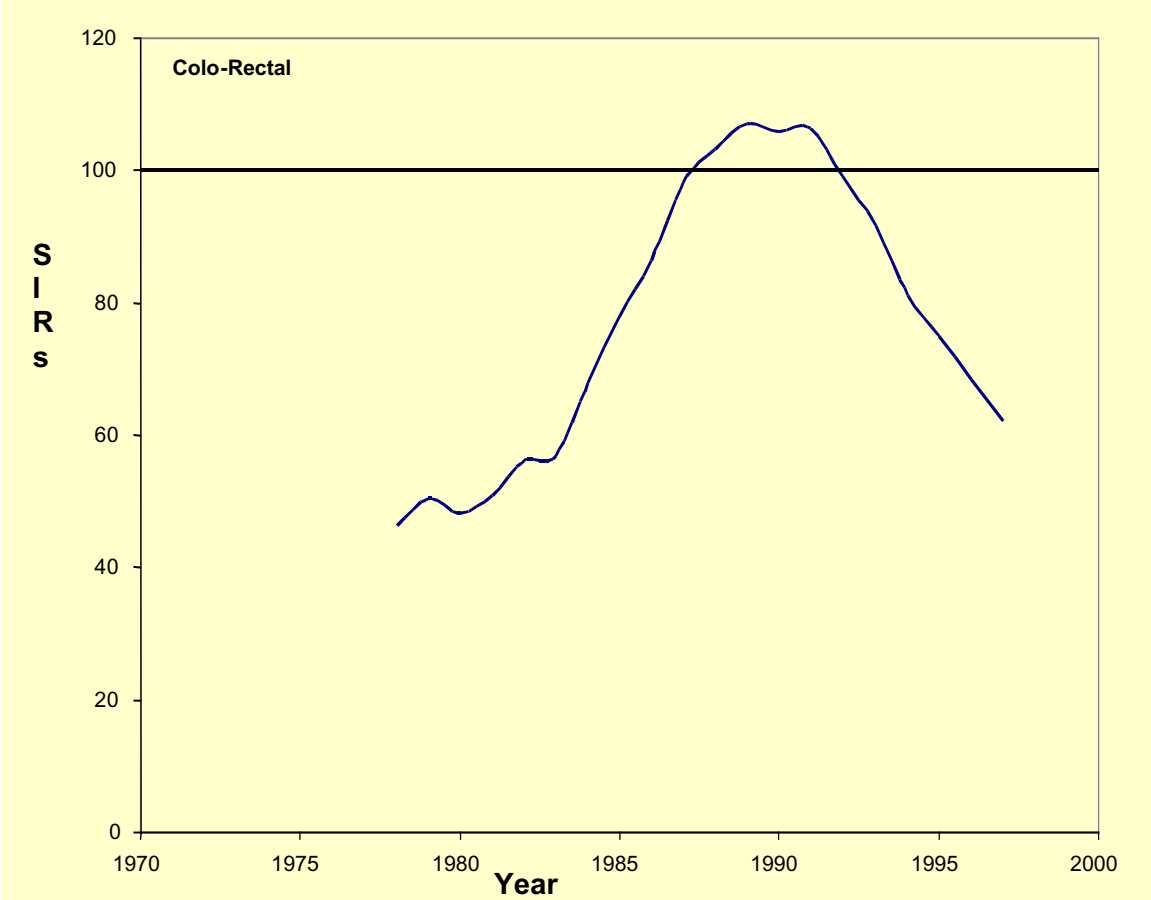
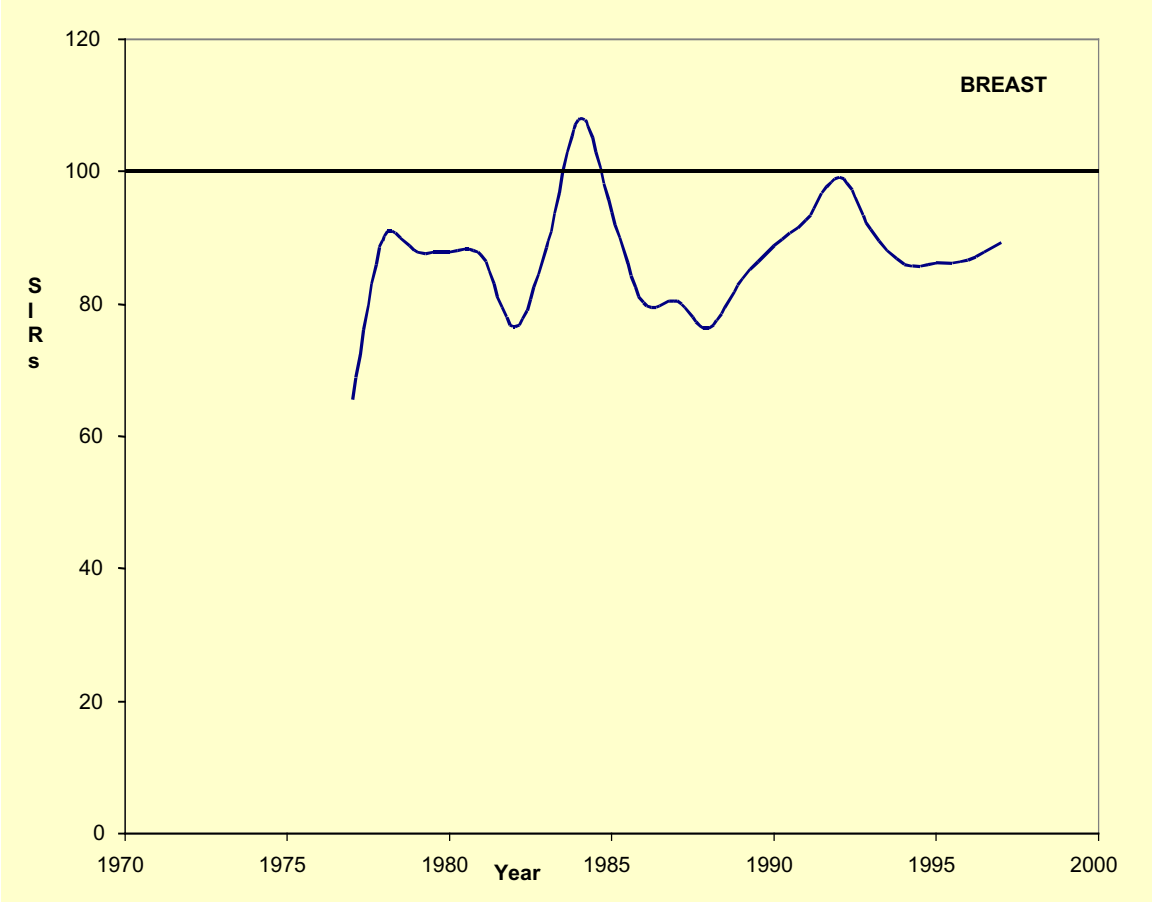


Figure 8

Standard Incidence Ratios (SIRs) for Combined Invasive and *in situ* Breast Cancer 1974-1997



Includes Invasive and *In situ* cancers

Figure 9

Standard Incidence Ratios (SIRs) for Invasive Cervical Cancer 1974-1997